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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/684,061	10/06/00	BARTELMEZ, S	0450-0031.30

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EXAMINER	
ZARA, J	
ART UNIT	**PAPER NUMBER**
1635	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/684,061	Applicant(s) BARTELMEZ ET AL.	
	Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

KATRINA TURNER
PATENT ANALYST

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed June 5, 2001, Paper No. 7.

Claims 1-20 are pending in the instant application.

Election/Restriction

SEQ ID Nos: 2-7 and 10-12 as pertaining to claims 1-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Applicant's election with traverse of SEQ ID NO: 1 in Paper No. 7 is acknowledged. The traversal is on the ground(s) that all of the originally claimed sequences of claims 1-20 should be considered a single invention by the PTO because it was determined previously at the PTO that ten sequences constitute a reasonable number of sequences for examination and furthermore that the searches required for examining the original breadth comprising multiple nucleic acid sequences representing individual molecules would not be an undue burden to the PTO or to the examiner. This is not found persuasive because, contrary to Applicants' assertions, the new restriction guidelines at the PTO require that Applicants choose a single gene for examination per invention as indicated in the original restriction requirement mailed April 27, 2001, Paper No. 6. The data bases which must be searched for a thorough examination of each nucleic acid molecule or gene are extensive and the search of more than one independent gene or nucleic acid molecule

places undue burden on both the PTO and the examiner because the different searches required for adequately examining the prior art for different genes would not be coextensive.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, 8, 13, 14 and 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially uncharged" in claims 4, 13 and 18 needs to be further defined or delineated.

Claims 5 and 14 refer to structures which are presented in figures. The claims must not refer to figures but must describe the claimed invention in language which is independent of references to figures.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to compositions and methods for treating a human cancer patient comprising the administration in vivo, or the infusion of an antisense treated stem cell containing population of cells following ex vivo transfection, of one or more antisense oligomers which are directed to an mRNA encoding any gene which is preferentially expressed in stem cells, whereby an increase in the number of lineage committed progenitor cells and their progeny in the peripheral circulation is observed in the patient and a diminution of cancer cell or solid tumor growth is observed in the patient.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene delivery in organisms. Branch and Crooke teach that the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in

treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using various vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of treating a cancer patient in vivo or ex vivo. The specification teaches the administration in vitro of SEQ ID NO: 1 to isolated murine hematopoietic stem cells whereby an alteration of phenotype is observed in the target cells. The specification fails to teach the treatment of any patients comprising the administration of antisense which target and inhibit the expression of any and/or all genes which are preferentially expressed in stem cells. One skilled in the art would not accept on its face the examples given in the specification of in vitro transfection into hematopoietic stem cell isolates of SEQ ID NO: 1, which targets the mRNA encoding Evi-1 zinc finger protein as being correlative or representative of the successful inhibition of cellular proliferation or increasing the number of lineage committed progenitor cells and their progeny in vivo comprising the administration of antisense oligonucleotides which target any and/or all genes preferentially expressed in stem cells, nor of being correlative or

representative of the successful treatment of any cancers in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of antisense in reaching and entering the appropriate target cell in vivo and subsequently inhibiting cellular proliferation of or altering the phenotype of target cells, or increasing the number of lineage committed progenitor cells in an organism or in treating cancers in an organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo or ex vivo delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed, which treatment methods are for cancer treatment in an organism.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods for treating a human cancer patient comprising the administration in vivo, or the infusion of an antisense treated stem cell containing population of cells following ex vivo transfection, of one or more antisense oligomers which are directed to any mRNA encoding a gene which is preferentially expressed in stem cells, whereby an increase in the number of lineage committed progenitor cells and their progeny in the peripheral circulation is observed in the patient and a diminution of cancer cell or solid tumor growth is observed in the patient. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring all target genes of the genus comprising any and/or all genes which

are preferentially expressed in stem cells, and further that treatment effects are provided. Since the specification fails to provide any particular guidance for the identification of all genes which are preferentially expressed in stem cells as well as the successful inhibition of their expression whereby cellular proliferation or tumor growth has been inhibited, or whereby an increase in the number of lineage committed progenitor cells has been obtained in an organism, nor for the successful treatment of any cancers in an organism, and since determination of these factors for a particular antisense targeting a particular gene which is preferentially expressed in stem cells is highly unpredictable, it would require undue experimentation to practice the invention claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Mitani et al.

Mitani et al teach a composition comprising antisense oligonucleotides which target the mRNA translational start codon of mRNA encoding Evi-1 zinc finger protein, comprising SEQ ID NO: 1, which gene is preferentially expressed in stem cells (See enclosed abstract).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitani et al as applied to claims 17 and 19 above, and further in view of Baracchini et al.

The claims are drawn to antisense oligonucleotides which target the translational start codon of genes preferentially expressed in stem cells, including Evi-1 zinc finger protein of known nucleotide sequence, and which antisense comprise substantially uncharged backbones and are nuclease resistant.

Mitani et al are relied upon as cited in the 102 rejection above.

Mitani et al do not teach modified antisense oligonucleotides which comprise substantially uncharged backbones and which are nuclease resistant.

Baracchini et al teach the incorporation of various modifications into antisense oligonucleotides for enhancing cellular uptake, target binding and nuclease resistance, including the incorporation of various modified internucleotide linkages which substantially reduce the charge of the backbone of the oligonucleotides compared to unmodified internucleotide linkages (See especially col. 6-9).

It would have been obvious to one of ordinary skill to design and test antisense oligonucleotides for their ability to inhibit the expression of nucleic acids encoding translational start codon of Evi-1 zinc finger, because antisense oligonucleotides which target the translational start region of Evi-1 zinc finger and inhibit the expression of this target gene were previously taught by Mitani et al. One of ordinary skill in the art would have been motivated to target this region of the Evi-1 zinc finger gene in order to inhibit Evi-1 zinc finger expression because it was taught previously by Mitani et al that aberrant expression of Evi-1 has been associated with chronic myelocytic leukemia. It would have been obvious to one of ordinary skill in the art to incorporate modifications into antisense oligonucleotides such as modified internucleotide linkages because such modifications had been successfully incorporated into antisense oligonucleotides for enhancing cellular uptake and increasing nuclease resistance. Therefore the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

July 27, 2001

ANDREW WANG
PRIMARY EXAMINER